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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,157	05/01/2001	Michael D. Smith	0942.5040001/RWE/MTT	2674

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/06/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,157	SMITH ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *4-6,8,9,19-23,25 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,10-18,24,26-28 and 44-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement filed November 2, 2001 and June 25, 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112 – New Matter

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3, 7, 10-18, 24, 26-28 and 44-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Here, the new limitation of "with the proviso that said reverse transcriptase is not a Murine Moloney Leukemia Virus (M-MLV) reverse transcriptase with a methionine mutation at amino acid position valine 223" in claims 1 and 49 appears to represent new

matter. Also, the new limitation "not in the RNAse H domain" appears to be new matter and no basis was cited for this limitation. A careful review by the examiner of the specification, particularly at the pages cited by Applicant, failed to identify any support for this new negative limitation. As noted by MPEP 2173.05(I),

> "Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 112 – Written Description

3. Claims 1-3, 7, 10-18, 24, 26-28 and 44-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register:

December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID Nos. For example, even in claim 7, which is drawn to an MMLV reverse transcriptase which is altered at position 204 from a Histidine to an Arginine, there is no description in the specification of any MMLV reverse transcriptases which differ in sequence from the known prior art sequence. Also, claim 49, which is drawn to particular positions, clearly reads on any reverse transcriptase from any organism without the sequences of those enzymes being taught or suggested in the specification. Further, the claim permits any number of muations except the specifically excluded position 223 mutation. The broadest claim is drawn to any reverse transcriptase from any species with any sequence and any mutation. Thus the claims encompass a genus which comprises hundreds of millions of different possibilities since in a protein of about 671 amino acids there are more than 671^{19} possible single amino acid changes (this equates to about 5×10^{53} different possibilities). The number of possible changes becomes even more astronomical if multiple amino acid changes are permitted. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains are required. No structural limitations or requirements which provide guidance on the identification of sequences which meet the functional limitation of enhanced thermostability is provided.

Further, these claims encompass alternately spliced versions of the proteins, allelic variants including insertions and mutations, proteins which have a removable amino terminal end, while only specific amino acid sequence variants have been provided. No written description of alleles, of upstream or downstream regions containing additional sequence have been provided in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the thermostable MMLV reverse transcriptases lack any specific structure, which is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the wild type protein with the exemplified mutations, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to any reverse transcriptase which is modified for enhanced thermostability. In particular, while some claims define particular amino acids, such as the H204R change, the entire surrounding sequence of

600 amino acids is not defined in these claims, leaving only the particular change as a fixed point in what can be a protein of any sequence.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a reverse transcriptase with enhanced thermostability, without sufficient structure to meet this functional limitation.

In the instant application, certain specific SEQ ID NOs are described implicitly, though not explicit teaching of the complete sequence of a particular MMLV reverse transcriptase is found in the specification. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise the wild type MMLV reverse transcriptase as shown by the prior art sequence modified at the selected positions as having enhanced

thermostability. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 16, 17, 18, 24 and 26-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Blain et al (J. Biol. Chem. (1993) 268(31):23585-23592).

As an initial matter, the claims must be interpreted. The claims use terms such as "modified or mutated to increase or enhance thermostability", "reduced RNAseH activity", "reduced TDT activity", "increased fidelity" which are defined in the specification, but which definitions fail to provide any significant limitations because no standard for comparison is given. For example, on page 27, paragraph 0073, the specification indicates that "increased fidelity" is defined as, "preferably 1.2 to about 10,000 fold", but no comparison is given to any particular fixed standard. While the paragraph prefers to compare the mutant to the unmodified, this is not a limitation in the specification or the claim. Thus, these terms are read extremely broadly so that any enzyme which has, for example, "enhanced thermostability" relative even to an inactive truncated form is found to meet the claimed limitation under the broadest reasonable interpretation.

Blain et al teach altered MMLV reverse transcriptases which have expressly shown reduced RNAse H activity (see page 23588, table 1), retain DNA polymerase activity (see page 23588, table 1) and discusses that some fragments are inactive (see page 23591, column 2, last paragraph). Thus, relative to completely inactive fragments, the mutant MMLV reverse transcriptases shown by Blain have increased fidelity and thermostability while they have reduced RNAseH activity relative to wild type MMLV reverse transcriptase.

6. Claims 1, 12-18, 24 and 26-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Arakawa et al (JP 2000-139457, published May 23, 2000).

Arakawa et al teach altered MMLV reverse transcriptases which have expressly shown reduced RNAse H activity (see translation, page 2 of 9, paragraph 0008) which retains enhanced DNA polymerase activity (see translation, page 2 of 9, paragraph 0009) and expressly teaches thermostability at 60 C of the modified enzyme which retains significant activity at 60 C (see abstract and translation, page 6 of 9).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Blain et al or Arakawa et al, either in view of Stratagene Catalog (1988) p. 39.

Blain et al teach altered MMLV reverse transcriptases which have expressly shown reduced RNAse H activity (see page 23588, table 1), retain DNA polymerase activity (see page 23588, table 1) and discusses that some fragments are inactive (see page 23591, column 2, last paragraph). Thus, relative to completely inactive fragments, the mutant MMLV reverse transcriptases shown by Blain have increased fidelity and thermostability while they have reduced RNAseH activity relative to wild type MMLV reverse transcriptase. Blain teaches adding nucleotides and primers (see page 23586, column 2).

Arakawa et al teach altered MMLV reverse transcriptases which have expressly shown reduced RNAse H activity (see translation, page 2 of 9, paragraph 0008) which retains enhanced DNA polymerase activity (see translation, page 2 of 9, paragraph 0009) and expressly teaches thermostability at 60 C of the modified enzyme which retains significant activity at 60 C (see abstract and translation, page 6 of 9). Arakawa teaches the use of RT's in RT-PCR (see page 1 of 9 of translation).

Neither Blain nor Arakawa teach formation of a kit with these known reagents.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method and products of either Blain or Arakawa into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantitites of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantitites you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

Response to Arguments

10. Applicant's arguments filed January 16, 2003 have been fully considered but they are not persuasive.

Applicant argues that the specification provides a number of examples of reverse transcriptases along with functional characteristics and guidance on the types of mutations which applicant argues provides possession of the full scope of the invention.

These arguments are not persuasive because the claims lack structural limitations on the reverse transcriptases. To the extent that pages 8 and 9 show structure, the lists of mutations are not shown by Applicant to have any beneficial effects. Finally, as noted in the rejection, claim 1 defines the reverse transcriptase solely by function. This is expressly found inadequate in Lilly to define the genus and provide possession. The current case demonstrates an instance, as in Lilly, where the absence of a precise definition of the genus, here reverse transcriptases which are modified to have certain functions, is insufficient to comply with the requirement for written description. See Id. at 1569, 43 U.S.P.Q.2d at 1405. The patentee's claims in Lilly were drawn to a large genus of all vertebrate or all mammalian insulin cDNA, while the specification of the patents only provided the cDNA sequences for the rat or human insulin proteins. See Id. at 1563, 43 U.S.P.Q.2d at 1401. Lilly held that a generic claim limitation which involved chemical formula were usually properly described. However, in the case of materials identified solely by function with chemical structure, the Federal Circuit stated that "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." Id. at 1568, 43 U.S.P.Q.2d at 1406. Here, the definition of the reverse transcriptases operates solely on the basis of what the enzymes do, rather than what they are. Therefore, the written description rejection will be maintained.

Applicant then argues that the Blain reference is not a 102 because it does not teach a reverse transcriptase which has been mutated to increase thermostability. The Blain rejection is retained pending deletion by the Applicant of the new matter phrase

"not in the RNAse H domain". Similiarly, the Arakawa rejection and the 103 rejections are maintained pending deletion of the new matter. Currently, however, these rejections would not apply to the claims.

As noted above, the IDSs filed as paper numbers 7 and 8, November 2, 2001 and June 25, 2002, respectively, lacked copies of the references. The examiner took the additional step of checking the large IDS room to see if the IDS was misplaced but the IDS was not there either. The supplementary IDS filed January 24, 2003 was received and considered.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

February 6, 2003